beta-Lactam antibiotics are the most important antibiotics targeting the bacterial cell wall. However, their utility has been compromised due to broad resistance by bacteria to these antibiotics. Yet, their targets, penicillin-binding proteins (PBPs) still remain important targets for antibiotics. The importance of PBPs, especially the high-molecular-mass variants, is due to their critical functions in biosynthesis of bacterial cell wall. But equally important, these proteins decorate the surface of the plasma membrane, hence access by antibiotics is often less of a problem than is for the cytoplasmic targets. I will describe an in silico search for novel classes of antibiotics carried out with the X-ray structure of the PBP2a from methicillin-resistant Staphylococcus aureus (MRSA). MRSA is a global scourge, infections by which afflict 100,000 individuals annually in the USA alone. A significant proportion of these cases lead to mortality. Resistance to beta-lactam antibiotics in these organisms is overencompassing, including penicillins, cephalosporins, carbapenems, among others. I will describe discovery of the oxadiazole and quinazolinone classes of antibacterials, which target PBPs in MRSA. The lead compounds were elaborated synthetically into a library of several hundred members, which were screened for antibacterial activity. Both classes of antibiotics target bacterial cell-wall biosynthesis, they exhibit favorable pharmacokinetic properties, they are efficacious in a rodent model of MRSA infection and they are orally bioavailable. Both classes of compounds hold great promise in addressing clinical needs in treating infections by MRSA.

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